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Joint pain and quality of life; results of a randomised trial

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1 Eight hundred and forty-six patients with pain in one or two joints of the hip, knee, ankle or wrist participated in a randomised double-blind trial to compare the efficacy, tolerability and effect on quality of life of diclofenac sodium slow release (DSR) 100 mg daily and a combination of dextropropoxyphene 180 mg and paracetamol 1.95 g daily (D&P). Health status or quality of life was measured using the Nottingham Health Profile (NHP) questionnaire.

2 Pain as measured by a visual analogue scale (VAS) showed 8% greater pain reduction with DSR as compared with D&P ($P < 0.05$). Physical mobility as measured by the NHP improved by 13% more with DSR as compared with D&P ($P < 0.01$). Energy, sleep, social isolation and emotional reactions did not differ significantly between the two treatment groups, but both treatment groups showed improvement during the trial. More D&P patients as compared with DSR patients reported problems with their job of work ($P < 0.05$), and time lost from work ($P < 0.05$).

3 Patients on D&P suffered an excess of tiredness or sleep disturbance (50 *vs* 21, $P < 0.01$) whilst patients treated with DSR had an excess of abdominal or epigastric pain or indigestion (40 *vs* 18, $P < 0.01$). 57 patients were withdrawn from DSR and 65 from D&P.

Keywords quality of life health status joint pain non-steroidal anti-inflammatory drugs (NSAIDs) analgesics general practice

Introduction

There is much debate amongst clinicians about the best approach to the treatment of joint pain (Doyle, 1986). Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in general practice, but a combination of dextropropoxyphene and paracetamol (D&P) is also frequently prescribed. Problems with the two types of treatment involve, for NSAIDs, chiefly the gastro-intestinal side effects, and for dextropropoxyphene the chief concerns are the effects on the central nervous system. Whether or not an anti-inflammatory analgesic agent such as diclofenac slow release (DSR) can provide greater benefit than a simple analgesic such as dextropropoxyphene and paracetamol (D&P) is of concern to doctors and patients alike. In view of the current uncertainty in this field, it was appropriate to undertake a large trial to establish the relative benefits and risks of both treatments. This trial was conducted in general practice where most patients with joint pain are treated (Morbidity statistics from General Practice, 1981–1982).

Health-related well being, often referred to as 'quality of life' is important to patients with joint pain since their routine daily activities may be affected. It seemed possible that treatment could improve a range of outcomes relevant to patients' quality of life and that this could differ according to the treatment employed. The Nottingham Health Profile (NHP), a measure of health status, has been tested in various chronic disease states (Hunt *et al.*, 1981, 1982) and the study by Hunt *et al.* (1981) showed a high level

of reproducibility of this instrument in osteoarthritis. This made this instrument especially suitable for the present study. Ease of use further recommended it, as it is self-administered and can be completed by literate patients within 10 min.

Methods

Eligible patients were men and women aged 40–65 years who presented to their general practitioner with pain in not more than two joints, from hip region, knee, ankle or wrist. The pain had to be located in the joint, non-traumatic and non-infectious in origin, and not treated with a non-steroidal anti-inflammatory drug regularly within the previous 6 months. Patients who had a known history of peptic ulcer, liver or renal disease, or who were sensitive to NSAIDs were excluded from the study.

The trial was randomised and double blind and lasted for 4 weeks. After giving informed consent, patients were randomised to receive either DSR (Voltarol Retard one tablet each morning) plus placebo D&P (two tablets, 3 times daily) or placebo DSR plus D&P (Distalgesic) for 4 weeks. Patients thus received seven tablets daily.

At each visit the range of movement of the worst affected joint was noted (not limited, some limitation, or severe limitation). The worst level of pain in the previous 24 h was recorded with a colour-graded 10 cm visual analogue scale (VAS) (Grossi *et al.*, 1983), and the doctor enquired if the patient had any symptoms not related to the joint pain. The patients also completed the NHP questionnaire (Part I and Part II). In addition, patients recorded time lost from work over the previous week on account of joint pain. At the first visit the NHP was completed after seeing the doctor, but at subsequent visits it was completed before seeing the doctor.

Compliance was defined as taking at least 75% of the specified daily dose of medication.

The Mann-Whitney U-test and chi-square test was used to examine whether the two treatment groups were well matched for age and sex respectively. Patients' responses to NHP Part I gave results in six sections, sleep, energy, social isolation, pain, emotion, and physical mobility. High scores represent a greater reported disability. The results from NHP Part 1 were analysed using the Mann-Whitney U-test on baseline values and on changes from baseline. Chi-square test was used for limitations of movement. VAS was analysed using *t*-test.

Responses to NHP Part II were categorised as affirmative or negative and were analysed by partitioning a 2×4 chi-square test on 3 degrees of freedom into three chi-square tests with one degree of freedom each in order to test whether the proportion of positive and negative responders was the same in the two treatment groups. (The *P* values presented are for one of these chi-square tests on one degree of freedom for patients showing changes in the trial).

Results

Eight hundred and forty six patients were recruited by 368 general practitioners. The range of patients recruited by each doctor was 1–6, with a mean of 2.3 patients recruited. Forty-eight of the 421 who had been randomised to DSR were ineligible, as were 43 of the 425 randomised to D&P. Too many joints or the wrong joints involved accounted for 19 and 17 patients in the DSR and D&P groups respectively; 10 DSR patients and six D&P patients were outside the age criteria. Nineteen patients in each group had been recently treated with NSAIDs and one patient randomised to D&P had a joint effusion. This left 373 patients in the DSR group and 382 in the D&P group. Withdrawal during the study of 57 patients from the DSR group and 65 from the D&P group left 316 and 317 patients respectively completing the 4 week period.

The two groups were well matched for age and sex with 168 men and 205 women in the DSR group and 187 men and 195 women in the D&P group. Patients randomised to DSR had a mean age of 55 years and those to D&P a mean age of 54.6 years.

The worst affected joint was most commonly the knee (Table 1). Both treatment groups presented a very similar picture. The two groups were well matched on all clinical parameters except for pain as measured by the NHP ($P < 0.01$, see Table 4).

A similar proportion of patients withdrew in each group (15% on DSR and 17% on D&P). Reasons for withdrawal are categorised in Table 2. Gastro-intestinal side effects were a common reason for withdrawal in both groups. Central nervous system complaints were associated more with withdrawals on D&P (27 patients) than DSR (13 patients). Of the 39 side effect withdrawals on DSR, two were also withdrawn for inefficacy and three because they were better. The 42 side effect withdrawals on D&P also include one patient who was better and one patient who found the treatment in-

Table 1 Affected joints

Affected joints	*Worst affected joint*	*Other joint affected*					
		No other	*Knee*	*Hip*	*Ankle*	*Wrist*	*Totals*
DSR	Knee	97	75	24	17	6	219
	Hip	37	32	22	0	1	92
	Ankle	7	4	4	6	0	21
	Wrist	16	8	4	1	11	40
	Totals	157	119	54	24	18	372*
D&P	Knee	72	89	25	14	8	208
	Hip	43	34	20	1	4	102
	Ankle	11	5	0	4	0	20
	Wrist	18	6	5	0	22	51
	Totals	144	134	50	19	34	381**

* For one patient, worst affected joint not recorded – knee and wrist affected.
** For one patient, joints equally affected – knee and hip.

effective. Sixteen patients dropped out of this trial because they failed to attend the final visit for unknown reasons (Table 2). All 16 were alive and well when their general practitioners were contacted after trial closure, and none had reported serious adverse drug reactions.

Details of gastro-intestinal and central nervous system side effects, none of which were life-threatening, appear in Table 3. It can be seen that more diarrhoea, abdominal pain, epigastric pain and indigestion occurred in association with DSR than D&P ($P < 0.01$). CNS complaints, dizziness or light-headedness, and tiredness or sleep disturbance were more frequently reported by patients on D&P ($P < 0.05$ and $P < 0.01$ respectively).

Pain relief as measured by the VAS was better on DSR than on D&P (Table 4). DSR showed a reduction of 42% on the VAS as compared with 34% on D&P ($P < 0.05$). With the NHP the corresponding reductions were 54% and 45% respectively ($P = 0.13$). Pain as measured by the NHP was higher in the D&P group at entry compared with DSR. Any regression to the mean effect would therefore tend to produce a greater improvement in NHP scores in the D&P group compared with DSR. In fact the change tended to be greater in the DSR group.

Table 2 Withdrawals

Reasons for withdrawals	*Diclofenac slow release (DSR)*		*Dextropropoxyphene and paracetamol (D&P)*	
	Number of patients with each type of symptom	*Number of patients*	*Number of patients with each type of symptom*	*Number of patients*
Side effects:				
– Gastro-intestinal system	25		22	
– Central nervous system	13		27	
– Skin	3	39	4	42
– Genito-urinary system	1		0	
– Respiratory	2		1	
– Other	5		3	
Inefficacy		5		8
Other illness, including hospitalisation		0		5
Death (myocardial infarction)		1		0
Drop-out for unknown reason		7		9
Better		5		1
Totals		57		65

Table 3 Symptoms

	Week 0		*Week 1 and/or 4*		
	DSR	*D&P*	*DSR*	*D&P*	*Significance of DSR vs D&P*
Number of patients assessed	373	382	—	—	
Central nervous system symptoms:					
Number of patients with symptoms	11	9	48	93	$P < 0.01$
Number with:					
Depression/anxiety	1	1	8	9	NS
Dizziness/lightheadedness	3	0	14	30	$P < 0.05$
Headaches	5	2	11	15	NS
Malaise	0	0	1	1	NS
Tiredness/sleep disturbance	4	7	21	50	$P < 0.01$
Other	0	0	2	7	NS
Total number of symptoms	13	10	57	112	
Gastro-intestinal symptoms:					
Number of patients with symptoms	3	6	63	60	NS
Number with:					
Abdominal/epigastric pain or indigestion	1	0	40	18	$P < 0.01$
Constipation	2	1	7	8	NS
Diarrhoea	1	0	14	2	$P < 0.01$
Upset/distension/wind	0	2	8	9	NS
Nausea	0	1	24	33	NS
Other	0	2	3	1	NS
Total number of symptoms	4	6	96	71	

NS: Not significant

Table 4 VAS and Nottingham Health Profile, part I

Parameter	*Drug*	*At entry* n	*Mean (s.d.)*	*Change (Initial-Final)* n	*Mean (s.d.)*	*95% C.I. for the difference between changes for the two drugs*	*Significance of changes* P
Pain (VAS) (mm)	DSR	372	63.8 (19.6)	348	−27.0 (23.2)	−7.7, −0.9	< 0.05
	D&P	380	65.8 (19.9)	352	−22.7 (23.4)		
NHP (mean weighted scores)							
Pain	DSR	352	50.3 (25.6)*	328	−27.3 (28.2)	−6.7, 1.9	NS
	D&P	366	55.9 (27.4)*	333	−24.9 (28.5)		
Physical mobility	DSR	351	26.2 (17.8)	330	−10.8 (16.0)	−5.8, −1.0	< 0.01
	D&P	364	26.5 (18.6)	331	− 7.4 (14.4)		
Energy	DSR	352	25.8 (34.2)	329	− 9.9 (27.6)	−3.3, 5.7	NS
	D&P	366	29.9 (35.1)	331	−11.1 (30.4)		
Social isolation	DSR	354	6.0 (15.3)	333	− 1.4 (11.7)	−1.3, 2.7	NS
	D&P	367	7.7 (18.0)	333	− 2.1 (14.4)		
Emotional reactions	DSR	349	15.1 (21.1)	326	− 7.1 (17.3)	−3.7, 1.7	NS
	D&P	357	16.8 (20.5)	322	− 6.1 (17.7)		
Sleep	DSR	353	29.0 (28.6)	333	−12.4 (25.2)	−4.0, 4.2	NS
	D&P	363	32.7 (31.4)	332	−12.5 (27.3)		

NS : Not significant *$P < 0.01$ for between drug comparison at baseline.

Responses to the question on limitation of movement showed a significant advantage to patients on DSR with 120 patients improving, 222 not changing and seven deteriorating. The figures for D&P were 86, 258 and 8 respectively ($P < 0.05$). For mobility changes as measured by the NHP, DSR with an improvement of 41% was significantly better than D&P with an improvement of 28% ($P < 0.01$) (Table 4).

Other sections of the NHP, energy, emotional reactions, social isolation and sleep, did not reveal any differences between the two treatments (Table 4).

Health related problems reported in Part II of the NHP are summarised in Table 5. Figure 1 shows the percentage of patients improved or deteriorated at the end of the trial. During the study period more D&P patients as compared with DSR patients developed problems with their job of work ($P < 0.05$), and time lost from work ($P < 0.05$).

87% of patients were compliant with DSR as compared with 78% with D&P.

It should be stressed that the results presented above are based on a comparison of the two agents at a single dose level, and altering the dose of either agent could alter the results in terms either of efficacy or side effects.

Discussion

The clinical assessment of disability in general practice is usually rather informal (Knox, 1986). The Nottingham Health Profile has been used by various workers in the field of arthritis. (Hunt *et al.*, 1981, 1982; Stevens, 1986). It was initially developed as a population survey tool (Hunt *et al.*, 1986), but is being used increasingly for evaluation of treatment. It has been criticised as being insensitive to mild degrees of illness (Hunt *et al.*, 1985).

In this trial the NHP differentiated between the two treatments used, for physical mobility improved more on DSR than on D&P; in addition, patients on DSR had less problems with work than did patients on D&P. These treatment-specific benefits, however, were not reflected in other areas of patients' lives as measured by the NHP. This may be because other NHP sections are insensitive to these benefits, although patients on both treatments showed significant improvement in all NHP categories by the end of the trial, due either to the treatment or the benefit of trial inclusion or a combination of both.

It is possible that the sample could have been biased by exclusion of patients with known

Table 5 Nottingham health profile, part II and time lost from work

		Number of patients with				
Activity	*Treatment*	*No problems on either occasion*	*Problems on both occasions*	*Problems developed*	*Problems resolved*	*Significance of changes** P
Job of work	DSR	217	85	3	29	< 0.05
	D&P	200	108	11	25	
Looking after home	DSR	157	127	12	50	NS
	D&P	155	143	11	35	
Social life	DSR	227	59	17	43	NS
	D&P	213	83	12	37	
Home life	DSR	294	22	7	22	NS
	D&P	284	29	14	19	
Sex life	DSR	288	34	3	15	NS
	D&P	277	37	10	16	
Interests/hobbies	DSR	200	104	10	29	NS
	D&P	168	117	14	43	
Holidays	DSR	260	53	7	26	NS
	D&P	249	52	12	31	
Time lost from work	DSR	263	37	3	26	< 0.05
	D&P	253	42	16	26	

* For patients showing changes in the trial. NS: Not significant

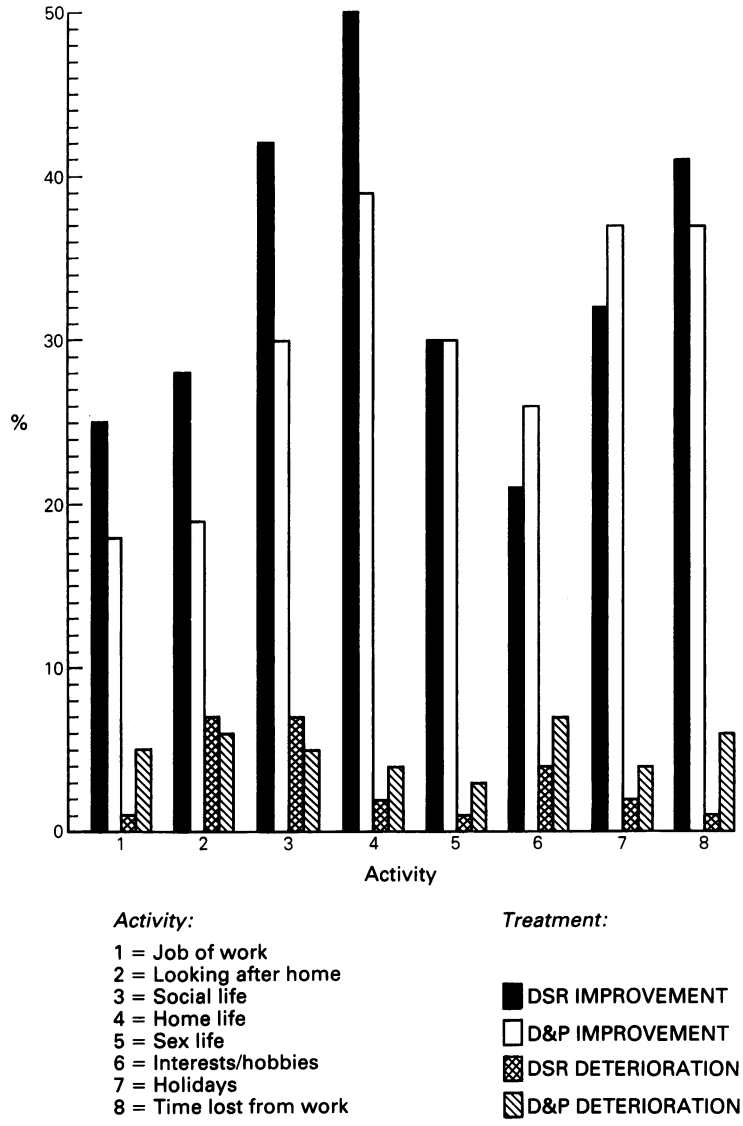

Figure 1 Percentage of patients showing improvement and deterioration in various activities considered in NHP part II.

hypersensitivity to NSAIDS without similar exclusions for D&P. However, there is no evidence that patients with such hypersensitivity (a very rare phenomenon) were included in the sample.

A surprisingly high proportion of patients in both groups reported no problems due to health in various aspects of everyday life. For some patients the side effects of treatment might outweigh benefit. More patients on D&P developed problems with their job of work and lost time from work compared to DSR. A similar trend is also seen in sex life (although this was not significant). It is possible that CNS symptoms account for these differences. A high reporting of tiredness or sleep disturbance and dizziness or lightheadedness was associated with D&P. CNS effects on quality of life have previously been reported in a trial of anti-hypertensive therapy (Croog *et al.*, 1986) where patients on methyldopa showed a greater deterioration in their sex life and work performance, than did patients on captopril.

Bombardier *et al.* (1986) in their extensive

study of quality of life in auranofin therapy in patients with rheumatoid arthritis have shown that treatment over 6 months can improve a range of outcomes relevant to patients' quality of life in rheumatoid arthritis. The time frame of Bombardier's study, whilst suited to rheumatoid arthritis, would probably be too long for our type of patient. Nonetheless, the duration of our trial may have been too short to detect all between-treatment differences that might emerge in the longer term.

It seems reasonable to suggest that it was the relief of joint pain which produced the improvement in mobility measured by the NHP. This instrument differentiated between the treatments used in two large groups of patients (even though the differentiation was not apparent in all sections and all aspects of life style). A smaller trial may have lacked the power to detect these differences. Many centres were needed to recruit sufficient patients who satisfied the criteria for this trial and it is of interest that in The Norwegian Multi-centre Study (Husby, 1986) of osteoarthritis 311 physicians were needed to undertake a comparison of two non steroidal anti-inflammatory drugs.

More difficulties may arise in making rheumatological diagnoses in primary care than in hospital practice; however, patients with trauma, or known rheumatoid arthritis were excluded from this trial, and the patients had many of the clinical features of osteoarthritis. The general practitioner frequently formulates a plan of action for such patients without recourse to X-rays (Knox, 1987). Osteoarthritis produces classical radiological changes but the diagnosis is only made when both symptoms and radiological changes are present and other possibilities (e.g. polymyalgia rheumatica, hypothyroidism) have been considered and excluded. The pattern of joint involvement seen in this trial mirrors that seen in osteoarthritis, suggesting that the bulk of pathology in this cohort of patients was likely to have been osteoarthritis. The better response of patients in this trial to an anti-inflammatory drug, rather than to simple analgesics suggests that inflammation may have been a factor in the majority of patients. An important inflammatory element in osteoarthritis is no longer thought to be in doubt (Fawthrop *et al.*, 1985; Gedikoglou *et al.*, 1986).

It is possible that slightly better compliance with the morning tablets rather than those intended for later in the day may be partly responsible for the better results obtained with DSR. Work by Doyle *et al.* (1980) has shown an advantage for NSAIDs over D&P in osteoarthritis in terms of joint tenderness, measured by means of an articular index, but Doyle *et al's* (1980) study failed to show any advantage for the NSAID (ketoprofen) in terms of pain relief. Ketoprofen was administered three times daily, but no comments on compliance were made in the trial report.

Comparison between the baseline NHP scores in this trial and the baseline scores noted by Stevens (198?) in 96 hospital out-patients with rheumatoid arthritis, showed similar pain scores. This suggests that the level of joint pain treated by general practitioners in our trial was of a comparable magnitude with that reported by Stevens (198?).

Prescribers need to balance the risk-benefit ratio of all therapies for individual patients. Significant benefits have been shown to be gained in terms of pain relief, improvement in mobility, and reduction in time off work by the use of diclofenac slow release as compared to dextropropoxyphene combined with paracetamol, in the context of this trial. Major adverse drug events were not observed in this trial and on a larger scale and over a longer period such events as respiratory depression with D&P overdosage would have to be contrasted with any more serious gastro-intestinal consequences of DSR.

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